Original Article

The INFUSE-Morphine Study: Use of Recombinant Human Hyaluronidase (rHuPH20) to Enhance the Absorption of Subcutaneously Administered Morphine in Patients with Advanced Illness

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Abstract

Morphine is often administered by the subcutaneous (SC) route when venous access is difficult to achieve. Hyaluronidase temporarily increases the permeability of SC connective tissues by degrading hyaluronan and has been shown to increase the dispersion and absorption of coadministered molecules. Therefore, hyaluronidase could enhance the pharmacokinetics of subcutaneous morphine. This Phase IIIB, double-blind, randomized, placebo-controlled crossover study compared the pharmacokinetics, safety, and tolerability of morphine administered SC with and without 150 U of recombinant human hyaluronidase (rHuPH20) with those of intravenous (IV) morphine administration in 13 patients in a hospice or palliative care setting. Each patient received morphine 5 mg parenterally daily for three days by a different method each day: IV, SC plus rHuPH20, and SC plus placebo (normal saline). The primary endpoint was the time to maximum plasma concentration (T_{max}) for morphine. Concomitant SC administration of rHuPH20 enhanced the absorption rate of morphine compared with SC morphine with placebo, significantly reducing the mean T_{max} from 13.8 to 9.2 minutes, a 33% decrease ($P = 0.026$). The respective values for geometric mean maximum plasma concentration were 94.9 and 107.5 nmol/L, a 13% increase ($P = 0.024$), and the area under the plasma concentration vs. time curve values

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Clinical Trial Registration: www.ClinicalTrials.gov, Identifier: NCT00593281.

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were 7.7 and 7.2 μmol• min/L (P = 0.23). Morphine plus rHuPH20 appeared to be safe and well tolerated. In patients requiring opioid analgesia, SC morphine plus rHuPH20 provides pharmacokinetic characteristics that are superior to those of SC morphine alone. These positive results warrant further studies on analgesic efficacy of morphine delivered with rHuPH20. J Pain Symptom Manage 2009;38:663−672.

Key Words
Subcutaneous, M6G, difficult venous access, parenteral, hospice, hospice care, palliative care, pain, pharmacokinetics, interstitial

Introduction

Injectable hyaluronidase products may enhance the subcutaneous (SC) absorption of coadministered medications by temporarily depolymerizing hyaluronan, a highly hydrated glycosaminoglycan, which is a major barrier to diffusion and bulk flow in the SC space. Preclinical pharmacology studies of a recombinant form of human hyaluronidase (rHuPH20) have shown that it enhances the dispersion and systemic bioavailability of coadministered molecules up to 200 nm in diameter.[1] The extent of drug dispersion is proportional to the concentration of hyaluronidase injected and the volume of the coinjected material. The viscosity of tissues is restored to preinjection levels within 24−48 hours after injection of hyaluronidase.[1,2]

By facilitating the absorption of coadministered drugs, SC injection of rHuPH20 may provide an alternative method of administration that could reduce complications encountered in patients with difficult venous access (DVA), including those with catheter placement failure as a result of obesity; vein sclerosis, fragility, or collapse; or catheter malfunction. Complications that might be avoided include multiple needlesticks, catheter-related venous thrombosis, infection, port-related complications, and extravasation injury.[3−5]

Morphine is commonly used to treat moderate to severe pain and is the standard against which all new analgesics are measured.[6] Often delivered intravenously (IV), morphine is the first-line medication for patient-controlled analgesia, both postoperatively[7] and for patients with advanced illnesses such as cancer.[8] SC delivery of morphine does not require venous access, reduces the likelihood of infection, precludes the need for close supervision owing to the less-invasive nature of administration,[9] and is less costly to administer.[8] Given sufficient time, SC-administered morphine has been shown to be as effective as IV morphine for palliative care in cancer patients.[8,10] We hypothesized that coadministration of rHuPH20 with morphine would enhance drug absorption, thus altering SC morphine pharmacokinetics to more closely resemble the IV profile. To test this hypothesis, we designed the INcreased Flow Utilizing Subcutaneously Enabled Morphine (INFUSE Morphine) studies to determine the pharmacokinetics, safety, and tolerability of morphine administered SC, with and without rHuPH20, compared with IV morphine administration. The trial reported here was conducted in patients requiring opioid analgesia. A complementary trial of morphine pharmacokinetics in healthy volunteer participants follows.

Methods

Study Design and Patients

This Phase IIIB, double-blind, randomized, placebo-controlled study involved 13 patients in a hospice or palliative care setting. A three-way crossover design was used (IV morphine, SC morphine with placebo, and SC morphine with rHuPH20), with each patient serving as his or her control. The study was approved by the appropriate institutional review boards (IRBs). Each patient signed an IRB-approved informed consent form and was reimbursed for the cost of time spent in the study. The study was not blinded with respect to IV vs. SC morphine administration, but it was double blinded with respect to SC